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Etiology of migraine

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THE ETIOLOGY OF MIGRAINE

BY

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THE ETIOLOGY OF MIGRAINE

INTRODUCTION

Migraine is of unknown etiology but certain theories have been advanced as to its probable cause, most of them incapable of proof. At the present time there is no satisfactory explanation of the symptoms of migraine; i. e., there is no one explanation which is universally accepted. In fact, at the present time the literature on migraine has assumed formidable proportions, and there is a great diversity of opinion on the subject. This paper, therefore, is intended only as a review or resume of the various theories which have been proposed in regard to the etiology of migraine. No personal comment or evaluation has been attempted. The theories of historical interest, and the significant theories of the present day together with the attempted proof of each theory are merely cited, together with an introductory section on definition and symptomatology of migraine.

DEFINITION AND SYMPTOMATOLOGY

Grinker (28) defines migraine in the following manner:

"It is an affection characterized by paroxysms of intense pain, usually in the head, preceded or accompanied by characteristic sensory or motor disturbances or their combination, along with general vasomotor and psychic phenomena. Although frequently appearing combinations of symptoms may be described as the most usual type of paroxysm, great variability is shown in the attacks of individual patients, all of whom are, however, symptomless between attacks." And according to Riley (47) "In the great majority of cases migraine may be described as a periodic incapacitating headache culminating in nausea or vomiting, often preceded by visual disturbances, followed by sleep and occurring against a background of relatively perfect health." A point in the definitions to be emphasized, however, is that the patient is symptomless and in apparently good health between the attacks. A typical attack, as described by Grinker (28) is as follows: "A foreboding of the impending headache usually appears. This so-called aura is, in reality, part of the attack and is relatively constant in character for the individual, so that he is forewarned of the oncoming distress. The patient may feel generally ill in health and under a strange feeling of anxiety and depression. Tiredness, sensations of heaviness, slowness of thinking or chilliness may be experienced for twenty-four hours before the headache. On the other hand, some individuals have a sensation of intense well-being, in some cases even euphoria or excitement. They

see more clearly and are alert and active. Other premonitory signs are vague, generalized tingling and numbness, gastric pain, nausea, appearance of goose-flesh and transient scotomata and flashes of light.

"The headache, itself, has a crescendo type of intensity, gradually increasing to an intense height. It is variably described as dull and boring, pressing, throbbing, hammering, viselike or lancinating. The pain begins at any point in the head, spreading to involve one entire side, or even becoming generalized. However, the most frequent site is in the neighborhood of the eye, either above, lateral or in deep. The sensation of a boring pain behind the orbit is quite common."

"Gastro-intestinal symptoms during the headache are so frequent in occurrence that they have given rise to the common appellation of sick-headache. Nausea is seldom missed and is associated often, but not always, with vomiting which persists to the point of bile emesis; hence the term bilious headache. The vomiting may be intractable for some hours and prevents the administration of the analgesics usually given by mouth. Other patients vomit at the apparent height of their pain, following which, recovery begins, so that vomiting is said to give them relief. There is a complete anorexia during the headache. Abdominal pains are also not infrequent and constipation is the rule."

"During the headache, the patient is mentally very slow and extremely irritable. His face is pinched or dull and expressionless. There is usually a general hypersensitiveness

of all sensory organs and he may be extremely restless. This especially is shown by a photophobia and abhorrence of noise which causes the patient to take to bed away from sound and light. General somatic impressions are magnified so that the patient attempts to lie quietly in bed. Superficial tenderness of the head may be so great that women cannot bear the weight of their hair."

"Signs referable to the cervical sympathetic nerves are often notable. Early a pallor of the face on one side; later a hyperemia and hyperidrosis of that side may be seen. One pupil may be smaller than the other and fail to react normally. General sympathetic dysfunction is evidenced in a bradycardia, generalized perspiration, frequency of urination and, in children, pyrexia."

HISTORICAL

"If one should search for the human ill which has manifest itself most widely during all times and among all peoples, there can be but little doubt that headache would attain this unenviable distinction. It is not surprising, therefore, that one form of this disorder, migraine, perhaps the most baffling and dramatic form of pain in the head should have acquired recognition as a definite symptom-complex early in medical history. The earliest allusions to pain in the head and face, as might be expected, present an obscure and confused picture, with but little tendency to classification or discrimination."--Riley (47).

Migraine was first differentiated and described accurately by Aretaeus of Cappadocia, toward the end of the first century of the Christian era. Because of the character of the headache, the symptoms frequently being one sided, he called the condition "Heterocrania". About fifty years later, the term "Hemicrania" was introduced by Galen, who attributed headache not arising from organic disease, "to the noxious vapours arising from the stomach, or other diseased parts." At this time, both Galen and Hippocrates attributed diseases to a "sympathy, or consent of parts". However, they did not explain this "sympathy" as taking place through the medium of the nerves. From this descriptive origin, the name has passed through a series of progressive modifications which have materially altered its form, several alterations being made during its adoption into the various European languages; the French "migraine", the German "migran", and the English "megrim". Today, the French term

"migraine" has acquired almost universal acceptance, and is now accepted as standard usage among English speaking people. On account of the symptoms, the laity has given the affection the popular names of sick headache, blind headache, and bilious headache, (partly due to the fact that bile is often vomited, and partly from the old humeral theory of pathology which regarded the bile as one of the chief morbidic fluids of the body).-- Gower (27), and Riley (47).

The following historical discussion is composed of excerpts taken from a paper written by Riley (47) : The Hippocratic school made no attempt to classify or distinguish between the many types of headache and pain about the head. Celsus who flourished under Tiberius, (14-37 A. D.), about one hundred and fifty years before Galen, described headache as an acute and dangerous distemper, but he had nothing to offer in differentiating the various types of headache, nor did he contribute to the task of contributing to its etiology. To Aretaeus (30-90 A. D.) however, is due the credit of having given the first description of a condition which may be accepted as representing the type of headache now called migraine. Although he described the various areas in which the headache may appear and its familiar radiation to other parts of the head, Aretaeus did not distinguish between these paroxysmal attacks of headache and the periodic occurrence of pain such as is found in neuralgia and in the migrainous attacks now recognized as symptomatic of some other underlying disease. He displayed no interest whatsoever in the causation of the symptoms or the

location of the disturbance.

Galen (A. D. 131 - 201) on the other hand, was particularly concerned with the etiological factors and the anatomical site of the disturbance which produced the pain. He described the vascular connections between the extra and intracranial circulation by which the vapors and humors which fill the intracranial cavity to excess may find an exit. He believed that the source of the headache lay in disturbances in various parts of the body which dispatch liquids or vapors containing harmful qualities to the brain. Galen also described the vomiting of bile in association with the headache and ascribed it to a sympathetic action of the intestinal tract with the head, the connection between the two structures being supplied by the great nerves which stretch between the stomach and the brain. His ideas of the pathogenesis of the disorder were based upon the humoral hypothesis and the influence of black bile upon the brain.

Serapion (A. D. 1070) produced a Galenic compendium in which headache was described and its production attributed to the various harmful hot or cold effluvia formed in the digestive tract and transported to the head.

The Renaissance was not productive of any real or definite advance in the scientific study of headache or the further identification of migraine. From time to time, however, treatises showing independence of viewpoint and some originality make their appearance. Among these was a work on migraine by Fernel (1497-1558) which had great influence. The author classified

the disorder systematically and described the symptoms clearly. He recognized the fact that headache was not a disease but only a symptom and should be studied as such. He located the site of the disturbance in the cerebral substance and its canals and passageways. In place of the irritating vapors and liquids blamed by the ancients, the bile bears the onus of producing the symptoms. The epigastrium and the organs of this part of the body were held accountable for the disorder of the bile.

The most outstanding contribution of the seventeenth century was that of Charles Lepois. The value of his contribution lies in the fact that the description is autobiographical, and that the symptoms are given in great detail and put down in logical order. After having carefully and accurately described the occurrences during an attack he then proceeded to formulate a theory of the causation of the disorder based upon serous effusions provoked by winds from the west and the approach of rain-storms. Many other contributions of this period contained classifications and groupings which succeeded only in making the situation more complicated and confused. Many conflicting theories of mechanical difficulties, inflammations, modifications of the caliber of the vessels and changes in the blood corpuscles, spasm or atony, plethora or anemia, were advanced as explanations for the pain.

In 1726 Wepfer published his observations concerning the internal and external affectations of the head. He expanded the ideas of Lepois and explained the hemicranial irritation by a condition of stasis of the blood, relaxation of the

vessels, and impeded resorption of the fluid. He thus made some approach to modern ideas, although he had no demonstrable structural basis for his theory since no vasomotor apparatus had been recognized at that time.

Thus, the chief contributions of the Middle Ages and the Renaissance to the understanding of migraine were in the field of symptomatology. The clinical conception of the disorder was fairly well established, and many of its characteristics were recognized and tabulated. No real advance was made, however, in determining the causation of the disorder.

The appearance of the contribution by Tissot may be considered to mark the beginning of the modern era as applied to the conception and study of migraine. The description of migraine in Tissot's publication marked a departure from the traditional dogmatisms of earlier writers. He offered reasonable hypotheses supported by logical arguments. It was his belief that the irritation passed from the stomach to the trigeminal nerves, but in what manner he did not know. He explained the many symptomatic manifestations of the disease as due to irritation of the nerves.

J. L. Morgan, (45) in 1825, divided headaches into three groups; i. e. (1) Those dependent on "plethora", and "derangement in the vascular system", (2) Those dependent on organic disease, (3) Those which arise from morbid sympathies. He places "hemicrania" in the first group, stating that there has been great diversity of opinion as to causes of hemicrania, some authors regarding it as a rheumatic, and others as an

intermitting febrile affection, but that he believes it due to a disordered state of the circulation, and that cases reported by Willis and Morgagni strongly favor this idea. In one of these cases, the patient had a violent hemicrania of a definite periodicity. He had tried all remedies in vain, but was finally relieved "by means of a slight decoction of the woods, which threw the patient into sweats". (This case was hereditary--the patient's mother had sick headaches.) In the case of the mother, bleeding relieved her attacks of headache, and the author feels that "the last circumstance strongly favours the opinion that periodical as well as rheumatic headaches arise from fullness, connected also with vascular activity". And in regard to the pathology of hemicrania he writes, "On a careful review of the pathological facts connected with headache, we are compelled to feel, that in spite of the diligence of the anatomist, and the zeal and sagacity of the clinical observer, our acquaintance with its true nature is very limited, and that very great obscurity still hangs over this interesting subject". Also, "That some change in the condition of the centre of the nervous system takes place even in these cases where the symptoms naturally arise from sympathy with distant parts, as the uterus, stomach, intestines, etc., seems extremely probable".

Claude Bernard, (6) in the middle of the 19th century, published a report of his investigation of the sympathetic nervous system and the results of his stimulation of the superior cervical sympathetic ganglion. Dubois-Raymond, (22) who him-

self suffered from migraine, found in the results of these investigations an essential correspondence with his own symptoms. He advanced the theory that migraine was caused by an irritation of the cervical sympathetic nerves which produced an angiospasm. For this reason he called the disorder a vasomotor neurosis. Mollendorf, (44), in 1867, considered the vasomotor disturbance to be angioneurotic in origin. In the same year, Jaccoud and also Eulenburg, (32), advanced the idea that the symptoms were either due to overaction or paralysis of the blood vessels, and predicated two types, one angioparalytic, and the other angiospastic.

In 1871, Henry G. Wright (56), wrote, "The periodic headache, known by the common name of Megrims seems to hold a position between the Nervous headache and the Brow-ague. On carefully tracing back the pain to its commencement, there can frequently be detected some trivial and half-forgotten cause which sufficed to produce the first attack. The same influence being repeated, probably established the periodic character of a first few seizures. Among such causes have been recorded, watching for several successive nights; periodic anxiety of mind; exposure for a certain time to a current of cold air, as in an office or whilst riding in an open carriage; sitting always on one side of the fire, persons of sedentary habits thus rendering one side of the face more tender and susceptible to cold. The subsequent regularity of the attacks and their continuance after the cessation of the influence that originally gave rise to them, is a striking illustration

of that periodicity in disease which has, of late years, attracted much attention".

"Light and noise increase the pain, which is often described as resembling an opening and shutting of the skull. In rare instances it has been found that a splitting of the skull by separation of its bones has actually taken place during the agony of the pain". Many persons suffer from severe headaches only during the prevalence of a north or north-east wind. He also makes the statement that sick or bilious headaches are more frequent during the summer and autumn, and that persons of dark complexions with black hair and melancholy dispositions are most subject to them.

Samuel Wilkes (55) published an article in 1872 on sick headache, in which he stated that he had taken particular interest in it because he had been a "martyr to it all his life." He recognizes and speaks of a type of headache "in particular idiosyncrasies, from eating some special article of diet, and which, probably has a gouty origin", but he does not class these headaches as sick-headaches. He states that sick-headache is a "purely nervous affectation, and due to a peculiar nervous temperament". He recognizes that it is, for the most part, hereditary. He states also that, "The true cause, then, of sick-headache lies deep in the patient's idiosyncrasy, and is developed by a hundred different causes. Whatever produces a strong impression on the nervous system of such a one pre-disposed will cause an attack", and he lists such stimuli as: A visit to the theater; A dinner party; Altered temperature of

the air; Loud noise; Odors of various kinds; or even the taste of certain substances, as well as various moral causes and worry. "The various influences spoken of, acting through the different parts of the nervous system, impress immediately the sympathetic, and so alter the current of blood through the head; thus while the face is pale, the larger vessels are throbbing, the head is hot, and the remedies which instinct suggests are cold and pressure to the part". As to pathology, it is the author's belief that sick-headaches are a result of a vascular derangement, which is secondary to an upset or an imbalance of the sympathetic nervous system, which is induced in predisposed individuals by certain stimuli, such as prolonged mental work, mental excitement, worry, grief, anxiety, passion, etc. (He also observes that the attacks are more frequent in females at or after the catamenial period.) These predisposed individuals, he observes, are always more or less anemic, or else they possess a general lack of tone of the muscular and arterial systems, with a slow, and soft pulse which is easily accelerated after slight exercise or excitement. These individuals are of a "nervous temperament", their brains are excitable, their senses acute, and their imaginations free". He also observes that it is curious that the attacks are not developed during mental excitement, but afterward when the excitement has passed off and the mental strain somewhat lessened. As to the role of the sympathetic nervous system in producing these sick-headaches, the author says, "We possess, besides the cerebro-spinal system of nerves, a sympathetic nervous system, the ganglia of which

can conduct, transfer, and radiate the effects of impressions; their power being controlled and regulated by the superior force in the cerebrospinal centres. Let the general tone of the body be lowered, and with it the regulating power of the brain be impaired, then the conduction and radiation of impressions through the sympathetic ganglia are no longer interfered with, and, instead of tranquil, even harmonious action in the various organs, as in perfect health, we have convulsive, excited, and painful movements. -----that we have contraction of the vessels of the brain, and so a diminished supply of blood produced by excited action of the sympathetic; and that the exhaustion of the sympathetic following on this excitement causes the dilatation of the vessels and the headache. There is no obvious reason why the sympathetic nerve of one side only should be affected, and therefore the disturbance of vision only affect one eye, except that in nervous disorders generally, such as chorea, epilepsy, tic douloureux, etc., one side of the body is often much more affected than the other."

Liveling (37), in 1873, published an extensive monograph on the subject of migraine, ascribing its symptoms to a "nerve-storm." He regarded the disorder as related to the convulsive state, and believed that one disturbance might pass over into the other. He implies that there is an accumulation of nervous force which explodes in the shape of a headache; and that it is certain that all who have carefully observed the phenomena leading up to an attack must have been struck with the excitement of manner and irritability which precede the outbreak. He

stated that worry is a common exciting cause in both men and women. He explains his theory thus: "On this theory then, the fundamental cause of all neuroses is to be found, not in any irritation of the visceral or cutaneous periphery, nor in any disorder or irregularity of the circulation, but in a primary and often hereditary vice or morbid disposition of the nervous system itself. This consists in a tendency on the part of the nervous centres to the irregular accumulation and discharge of nerve force--to disruptive and uncoordinated action, in fact; and the concentration of this tendency in particular localities, or about particular foci, will mainly determine the neurosis in question. The immediate antecedent of an attack is a condition of unstable equilibrium and gradually accumulating tension in the parts of the nervous system more immediately concerned, while the paroxysm itself may be likened to a storm, by which this condition is depressed, and equilibrium for the time restored."

In agreement with Liveing's theory of "nerve-storm" is Anstie (3), 1873, who writes: "Migraine is almost the only neuralgia of the period of bodily development, and depends on inherited defects in the nutrition of the medulla oblongata, and that it is intimately mixed up with, and frequently interchangeable with other and more formidable nervous diseases, which are also the results of similar defects in the nutrition of the medulla; and that it is, so to speak, a matter of chance whether a person born of a certain race will have migraine, or epilepsy, or asthma. In agreement with Dr. Liveing, I also am

obliged to reject the idea of sympathetic nerve disturbance as a primary phenomenon in migraine; I believe them to be only secondary."

William H. Day (18). 1883, also believed that the pain of migraine was of a nervous origin rather than due to a disturbance in the cerebral blood supply. He supported his belief with the following reasoning: "Nervous headache comes on sometimes when a patient dwells persistently on anything unpleasant, or is unable to remove his thoughts from it. This tires the brain, and disarranges the circulation within it; for the fact is now generally admitted that thought exhausts the nervous substance, as surely as walking exhausts the muscles." He observed that migraine is most frequent in women who are approaching the middle period of life, blaming the strain of maternal duties, menorrhagia, leucorrhea, dysmenorrhea, and even ordinary menstruation, as etiologic factors; stating that the ovarian irritation which prevails at the time of menstruation induces a painful condition of the cerebral nerves through a sympathetic action. He says: "The real disorder is in the nerve-fibers of the brain, which become deranged from distant sources of irritation acting through the sympathetic system. The vasomotor branches of the sympathetic nerve regulate the contraction and dilatation of the blood vessels of the brain; and we have seen that when the cervical sympathetic was divided, there was an afflux of blood and a dilatation of the vessels. When the vessels of the brain are contracted, the supply of blood is diminished; when they are

dilated the quantity is increased; and this is an explanation of the headache that results after the stage of excitement has passed, when the systemic circulation is heightened and increased."

Gower (27), 1888, is also strongly opposed to the theory that a vasomotor disturbance is responsible for the symptoms of migraine. Instead, he believes that they are due only to a primary disturbance or derangement of the sensory cells of some part of the brain substance. His argument against the vasomotor theory is as follows; "In order to satisfactorily explain the combination of symptoms which occur in migraine on the vasomotor hypothesis, it is necessary to assume: (1) An initial spasm of the arteries in a small region of the brain; (2) that the contraction always begins at the same place; and (3) that it can give rise to a definite, uniform, and very peculiar disturbance of function. However, these assumptions are not justified, because there is no evidence that the state of the surface vessels and accessible arteries is an indication of the condition of those of internal organs--therefore, the surface vascular changes which occur during an attack of migraine are not indicative of a similar vascular change occurring in the brain. Also, the surface vascular spasm which occurs, is bilateral in almost all cases, and it would follow that if both were the result of the same causative mechanism then the vasoconstriction which occurred in the brain would also be bilateral or general in nature, which does not fit in with the very frequent unilateral sensory disturbance which occurs in migraine." In support of the theory of the

cause of migraine being a primary derangement of the sensory cells of the brain, he proceeds as follows: "Emotional blush and pallor of fear are evidence that the vascular system is in a special way under the influence of the cerebral centers, and the vasomotor nerves are peculiarly sensitive to sensory impressions that are felt as pain, and therefore it is logical to assume that the vascular changes are the result of the disturbance in the nerve elements rather than the cause. As to the parts of the brain concerned in the production of the symptoms--loss of speech must be due to disturbed function of the cortex; the sensory symptoms in the limbs are similar to those which precede cortical disease, and this source is therefore probable. The hemianopia also is best explained by the assumption of deranged function in the occipital lobe, especially since right hemianopia may correspond to almost simultaneous aphasia, and the opinion is supported by the fact mentioned above, that hemianopia was fixed by a lesion in the cuneus. The cause of the headache is obscure. We know very little of the mechanism of this symptom in any condition. But when the pain is opposite in side to the sensory symptoms, we are obliged to assume that its seat is the cerebral hemisphere that is deranged; and the same conclusion is suggested when the pain begins on the side of the sensory disturbance, at some spot which has no definite relation to nerve distribution, as the very common initial seat, a small area in the temple. This is best understood by assuming a derangement of the sensory centers of the hemisphere which would receive impressions from this part.

There is evidence in many cases, of deranged function of lower sensory centers, those directly connected with the peripheral fibers--these are apparently the common seat of the disturbance in neuralgia. The nausea and vomiting throw no distinct light on the processes of the attack. We have seen, in many affections, how wide-spread is the central representation of the pneumogastric, and that vomiting may result from organic disease in any part of the brain."

Corning (16), 1888, disputed the theories of his contemporaries, just stated, that the pain of migraine originated in the substance of the brain, in the following manner: "As to the probable source of the pain in headache, it does not appear to be in the nervous matter of the cerebral hemispheres, or of the cerebellum, since no evidence of feeling has been obtained by vivisectors, till they approach the sensory ganglia, the thalami optici, and corpora quadrigemina. In fact, it is not even known if headache is of central origin, (i. e., if it originates in the parts of the brain where irritation causes symptoms of pain after the insensible greater hemispheres have been removed), or whether it depends on irritation of the filaments of the fifth nerve going to the dura-mater. Experiments upon the sensibility of different structures in the interior of the skull have given contradictory results; for whilst Leyden, Hitzig, and Ferrier have found the dura-mater to be highly sensitive, Pagenstecher ascribes a very low degree of sensibility to it, and Bartholow who experimented on the human subject, found it to be but slightly sensitive to

mechanical stimuli. The greater number of experiments seem to show that the pia mater is also not very sensitive, and the same may be said in regard to the greater part of the substance of the hemispheres. We are unable, again, from physiological considerations to explain why headache should be experienced when the intracranial disease is situated in so many different parts of the brain or its membranes; we must either admit that the tissues, which under ordinary circumstances are insensible or are only endowed with a low degree of sensibility, become sensitive under pathological conditions, and give rise to pain; or we may imagine that in diseased states the influence of pressure and irritation spreads to considerable distances, involving tissues that are sensitive. The dura-mater may undoubtedly be included amongst such sensitive structures, since it receives sensory branches from the trigeminus and vagus; perhaps the nerves of the choroid plexus, which Benedict has recently described, are of a sensory nature, and may be answerable for the "internal" headache sometimes complained of."

This concludes the significant work done on migraine up to the end of the nineteenth century. The significant work during the twentieth century will be considered in the next section of this paper.

THE MODERN THEORIES OF THE ETIOLOGY OF MIGRAINE

As to the heredity of migraine, in the words of Flatau (25), the individual is stamped at birth. No accurate statistics are at hand, but probably 50 to 80 per cent of migrainous patients have a directly homologous heredity. According to Riley (47), "The great majority of observers have placed the familial incidence of this hereditary tendency at 50 per cent or more in the sons and daughters born to affected parents." The transmission from mother to daughter is most common, from mother to son second in frequency. Balyeat (5a) assumes that approximately 7 per cent of the people in this country suffer from the symptoms of migraine, and that about 30 per cent of these manifest the symptoms before the age of ten, this being equivalent to about 2 per cent of the juvenile population. Walton, (54), consulting neurologist at the Massachusetts General Hospital, states that the "every-day type of migraine occurs in complete form in 17 per cent of healthy young adults, and in incomplete form in many more." The hereditary tendency of the disease and its transmission through the maternal protoplasm are stressed. Ely (24) states: "In substantiation of the contention that migraine is hereditarily transmissible, it is of interest to note that of 104 patients with migraine whose clinical histories have been utilized, 71.1 per cent gave ancestral histories of migraine, and 9 per cent gave histories of migraine on both the maternal and paternal sides, whereas of 100 normal persons, only 17 per cent revealed ancestral histories of migraine. And the

conclusion from the above figures (obtained from private patients and not from those of public or charitable institutions), is "A constitutional tendency to the development of migraine is transmissible from parent to offspring." Allan's (2a) observations are: Among 103 men, 56, or 54 per cent, gave a history of periodic headaches that could be clinically classified as definite migraine; 90 per cent of these gave a positive parental history; 48 per cent had both hemicrania and fluttering scotoma, and in 73 per cent the headaches had started before the age of 21. In addition, 13 had headaches that were too infrequent or too atypical to be definitely recognized as periodic migraine; but even in this group there was a positive parental history of migraine in 91 per cent. Among the 34 men without headache, there was a positive parental history in 29 per cent. Among the 92 wives, there were 50, or 53 per cent having a positive parental history, 55 per cent having hemicrania and 40 per cent fluttering scotoma, with the onset before the age of 21 in 85 per cent. In addition, there were 7 women with headaches too infrequent or too atypical to be recognized as migraine. A comparison of the frequency of typical migraine, atypical headaches and no headaches in the 103 physicians as compared with the 92 wives shows that the frequency of migraine is the same in the two sexes. Grinker (28) writes that in 80 per cent of patients, the first headache begins before the age of forty years. In over 50 per cent, the attacks begin between the ages of sixteen and thirty years. Gowers (27) stated that over one third of his patients suffered from headaches since a

period between five and ten years of age; however, puberty seems to be the most frequent time of onset, and that females suffer more than males in the ratio of 2.5 to 1. There is some disagreement in regard to the incidence of migraine in the different classes of society, and to the role that occupation plays as an etiologic factor. Allan (2) is of the opinion that "Among the ideas that have been handed down to us about migraine is the inclination to look upon it as one of the penalties of civilization and to consider it more prevalent in the upper classes, or among brain workers, than in the poorer classes, or those who labor with their hands. This idea that migraine is more prevalent in those whose brains are most highly trained and whose occupation is mental rather than physical, would be exceedingly hard to reconcile with the observed facts as to sex incidence and heredity in this malady." Allan (2) determined the occupation of a series of migraine sufferers, as compared with the occupations of nonmigrainous persons. The occupations of 400 migrainous patients have been tabulated as compared with the occupations of 1,000 nonmigrainous patients. After tabulating his results, he states, "As shown by the table, there is nothing in the writer's experience to indicate that occupation has any influence on the incidence of migraine." Kammerer (33) also believes that migraine does not confine itself to certain types of persons, for in his service the weak as well as the strong have been affected. On the opposite side of the fence on this question is Walton (54), who considers that migraine is an occupation neurosis. (Discussed more fully later in this paper.)

Among the great number of hypotheses advanced to explain the signs and symptoms of migraine are the following, which, according to Riley (47) and others, are the ones worthy of consideration at the present time:

1. The Vasomotor Theory.

The symptoms of migraine, to some degree, do suggest a vasomotor disturbance, either spasm or stasis. The sympathetic alteration seen in the paleness or hyperemia of the face, sweating, changes in the pupils and pulse rate, appear to be obvious evidences of changes in function of the cervical sympathetic function. The attacks come and go with such abruptness, leaving no trace behind them, that a temporary change in blood supply is a very attractive hypothesis to some. Furthermore, in the hypertensive states and the cerebral crises of arteriosclerosis, attacks are present which closely resemble migraine, but which, ultimately, lead to degenerative changes in the brain. In migraine, on the other hand, if prolonged spasm or stasis occur in so many attacks, it is surprising that so little damage results. The vasomotor theory fits the paroxysmal nature of the affection, its symptomless intervals, absence of cerebral pathology, and variability of its symptoms in different individuals. However, drugs which are notoriously vasoconstrictors and vasodilators, in a migrainous individual, do not bring on an attack, nor do they abort or stop the headaches.--Grinker (28).

In a paper written by D. K. Dickerson (20) in the Journal of Nervous and Mental Diseases, he is of the opinion that this vasomotor theory, as elaborated by Dubois-Raymond first, is

based upon sound physiological and anatomical principles. He feels that a vascular disturbance is the underlying cause and reports evidence of vascular disturbances often observed during the attack. Among these are the premonitory symptoms of facial pallor, often unilateral and, later, flushing and congestion of the face. Often the superficial temporal artery is hard and contracted and there is altered caliber in the retinal arteries. Bramwell (8) makes a suggestion that the symptoms of migrainous attacks can be accounted for by localized spasm and subsequent relaxation of the meningeal and cerebral arteries, while the headache is attributed to the re-establishment of the circulation and engorgement of the meningeal artery. He continues by saying that it is well known that the brain itself is entirely devoid of sensation, and that all intracranial pain and headache is registered by the dura-mater, this being supported by the fact that intracranial procedures may be painlessly conducted so long as there is no stretching or undue traction upon the meninges--even the dura-mater being relatively insensitive unless traumatized in the vicinity of the larger meningeal vessels. However, severe pain occurs if the meningeal artery is compressed. Also, the sole sensory nerve supply to the meninges comes through the trigeminus, and all intracranial pain, whether it be due to stretching of the dura from abscess, edema or blood clot, whether toxic, or whether due to engorgement of the middle meningeal artery, is all reflected via the fifth cranial nerve. He further states that it has been fairly well established that allergy has a definite relation to the

attacks of migraine in certain individuals, and this idea is not incompatible with the vascular theory when we consider that allergic influences may set in motion vascular changes. On the presumption that migraine is due to some fundamental disturbance in the stability of the vascular system, Dickerson (20) did ligations of the middle meningeal artery in several cases, in two of which, the ligation was necessary on account of a serious intracranial lesion. In the other cases, ligation was purposely carried out in the belief that by shutting off the major portion of the circulation to the dura on the involved side, some relief from the headache could be given--the purpose of this surgical procedure being for the relief of meningeal engorgement and subsequent headache. He states that his results were good on practically every one of the seven cases; and that he cites these cases to show that there is a definite relation between the headache of the so-called migrainous type and congestion of the middle meningeal artery.

Pasteur Vallery-Radot (52) favors the vasomotor theory also, to sustain which he recalls some of the symptoms accompanying the crisis, as pallor of the face, contraction of the temporal artery, sensation of constriction at the temples, transitory hemiparesis, paraphasia and visual disturbances and simultaneous onset of hemicrania and vascular spasms of other regions such as the retinal artery. He further states that the causes acting on the sympathetic nervous system, responsible for the vascular changes may arise from: (a) Anaphylaxis. (Pagniez, Nast, and Vallery-Radot having already shown the co-existence

and alternation of hemicranic crises with anaphylactic syndromes such as asthma, edema, paroxystic tachycardia.) (b) Endocrine disturbances, which can be divided into ovarian, thyroideal and hypophysial. (c) Thermic disturbances; after ingestion of special proteins, fat or other foods. (d) Reflex irritations. (e) Emotional upsets. Contributing causes such as insufficient sleep, alimentary disorders and atmospheric variations may be operative. The mechanism of the hemicranic crisis may be set in action by excitation of the sympathetic nervous system through the intermediation of a colloidaclastic shock, or direct excitation of internal or external origin. The sympathetic nervous system in hemicranic subjects may be found in a condition of congenital lessened resistance, but at times it is an organic disease, such as dysfunction of an endocrine gland, which is responsible for the dis-equilibrium of the vegetative nervous system. That hemicrania appears in the form of a crisis is explained by the fact that during the intervals the organism, by means of an unknown mechanism, gradually enters the condition in which the exciting cause will bring about an outburst.

Along the same lines as the above cited work of Pasteur Vallery-Radot is Braeucker's (10) paper on "The Anatomy and Surgery of the Vegetative Nervous System (), of which the following is an abstract. "Several types of operations were proposed for the relief of migraine. Starting with the conception that the individual attacks depend on a spasm of the cranial blood vessels, and that these blood vessels are innervated by the cervical sympathetic, operations were

performed on the one hand on the cervical sympathetic and on the other, on the perivascular nerve plexus of the internal and common carotid. Jonnesco resected the entire cervical sympathetic and reported good results. Witzel reported good results with periarterial sympathectomy on the carotid. The author operated on a man, who had suffered for twenty-five years from attacks of severe ophthalmoplegic migraine. He laid open the entire upper end of the upper cervical ganglion and, without doubt, sectioned the internal carotid nerve and the fibers ascending with the artery. The result was entirely negative. The attacks came on as before the operation, including vasomotor disturbances (a functional disturbance was carefully ruled out). Amyl nitrite relieved the pain for a minute. Hence, the blood vessels of the brain must have another innervation besides the cervical sympathetic.

"Sluder and Frasier reported that pain due to migraine is relieved by injections into the sphenopalatine ganglion. Braeucker only once found slight relief from such an injection of procaine hydrochloride; in two other cases it had no influence. The sphenopalatine ganglion, therefore, can have no important relation to the pain. Richter came to the conclusion that attacks of migraine may depend on spasm of the vertebral artery to which Foerster agreed. Twice during an attack, Braeucker blocked the vertebral nerves of the inferior cervical ganglion without any result. He then investigated all the cranial nerves. When the needle pierced the gasserian ganglion, the pain appeared and the patient cried out, "This is the real pain and such as I

have never had before." An injection of 0.5 cc. of alcohol developed an incomplete anesthesia and an attack which lasted eight days. Instead of affording relief it apparently caused an irritation of the trigeminus. When the same place was pierced again severe pain developed once more. Slow injections of 1.5 cc. induced complete anesthesia and the pain stopped. Later milder attacks occurred without the former associated symptoms, such as vomiting and vasomotor disturbances. The patient himself had the feeling that the nerve responsible for the attacks was partly under control. In two other mild cases of migraine the attacks were cut short by injection in the gasserian ganglion. The author again calls attention to the fact that the oculomotor, the trochlear, the abducens and especially the trigeminus are connected with the internal carotid through nerve branches. It is possible (especially in cases of ophthalmoplegic migraine) that the pain depends on a pathologic process in the trigeminal nucleus, the radiation of this process to the periphery over vascular nerve branches developing an abnormal vasomotor condition in the region of the internal carotid, which brings on the attack."

Pool and Nason (46) are also in favor of the vasomotor theory of the etiology of migraine. Their work was the observation of the effect of ergotamine tartrate on the arteries of the pia, dura, and skin of cats. The paper on the results of their work, and their conclusions, is summarized as follows:

"A. The effects of the intravenous administration of ergotamine tartrate on anesthetized cats may be summarized as follows:

(1) inconstant effects on the caliber of the pial arteries: (2) constriction of the dural arteries, the average decrease in diameter being 25 per cent: (3) constriction of the arteries of the skin (average 39 per cent): (4) elevation of the systemic arterial pressure: (5) elevation or no change in the cerebrospinal fluid pressure: (6) alteration in the venous pressure similar to that of the cerebrospinal fluid pressure: (7) decrease in the pulse rate.

B. Evidence from various sources suggests that the headache of migraine may be caused, in part, by the dilatation of the arteries in the dura.

Conclusion:

"On the basis of the experiments on animals here reported it is suggested that the clinical relief of the headache of migraine by the administration of ergotamine may be related to dural vasoconstriction. Of special interest is the difference in effect of ergotamine on the arteries in the pia, the dura and the skin."

However, Walton (54) who believes in the reflex theory of the cause of migraine, writes: "But the vasomotor changes, in my view, at least, are so far from constant that they are not to be taken into consideration in the search for causal factors, but are rather to be reckoned, when present, as among the comparatively unimportant accompaniments. This is the view long held by Gowers. The vasomotor symptoms are not only secondary rather than primary, but, in fact, they are not always present. All suppositions based on dilatation or contraction of blood

vessels as a primary cause of migraine lead to theoretical considerations which obscure rather than clarify our ideas of migraine. And, further, all such theories are based on a fallacy, namely, that contraction and dilatation of blood vessels necessarily cause pain. To confute this proposition, we need only remind ourselves of the extreme dilatation of blood vessels in the blush of shame or the turgidity of anger, on the one hand, and on the other hand, with the pallor of fear and faintness. Even the extreme degree of vascular spasm which results from cold produces numbness rather than pain." Walton also feels that the vomiting produces a general and special relaxation, just as fainting may appear at the height of pain, representing a protective effort on the part of nature.

2. The Reflex Theory.

The reflex theory postulates an irritation somewhere in the body which by its presence and continued activity results in attacks of migraine. The eyes have been blamed as one of the chief sources for reflex irritation. It has also been suggested that afferent vagul stimulation from the viscera produce head pains reflexly by radiation of stimuli into the neighboring trigeminal nuclei in the medulla and pons.

Didsbury (21) discards toxic, general, or even endocrinal theories as an explanation of migraine; he considers that it is caused by a local and superficial condition. The true cause of migraine must be sought in the presence of localized points of hyperesthesia, and he finds them along the course of the superficial nerves of the neck, cranium, or face and especially

at the point of emergence of the nerves. In these locations, lesions partaking of the nature of combined subcutaneous cellulitis, a myositis and an interstitial neuritis are present. The author says that the foci can be cured by massage and believes that when they are disposed of, migraine does not recur.

Walton (54), defining an occupation neurosis as "a condition resulting from overuse of certain parts," considers that migraine is an occupation neurosis, and involves (1) the visual centers; (2) the centers of accommodation; (3) the intrinsic and extrinsic muscles of the globe; and (4) the muscles outside the orbit which are called into play in the effort required for accurate vision, and also the muscles which serve to steady the head. Migraine results, in individuals of neurotic inheritance, from over-use, or use under the handicap of refractive error, of the parts concerned in vision. In cases of extreme susceptibility, migraine may even appear without error of refraction from moderate use of the eyes. He believes that the vasomotor phenomena are secondary, and that the vomiting "represents a protective effort on the part of nature." He further states, in support of the above theory, that "too many cases of migraine have been relieved, in part or entirely, by correction of refractive error, particularly of astigmatism, to be explained by coincidence. In the second place, attacks have been frequently aborted by the mere straightening of glasses, as I have many times verified in my own case. In the third place, migraine has lessened and disappeared in innumerable cases after accommodative paralysis has appeared. Finally, study of the blind shows that the greater the

blindness, the less the migraine. It may be objected that migrainous headaches are not quite unknown among the blind. But it must be remembered that it is a common practice for the blind, as for others, to adjust their accommodation to the distance of their work as judged, even in the absence of sight, by the position of their hands. He doubts that the pain of migraine is entirely intracranial--due to the non-sensitiveness of the dura. He thinks that perhaps the pain may be (1) the result of the "frown," or contraction of the brows which is possessed by astigmatics; (2) analgous to the pain which sometimes appears in the back of the neck and "base of the brain" after long continued eyework in which the head is held firmly in one position, this form of headache being muscular rather than intra-cranial. Thus he arrives at the conclusion that migraine may be an "occupation neurosis." He further states that his theory is not in disagreement with the theory that all migraine is due to a refractive error; nor in disagreement with the theory that there is a hereditary and constitutional basis for migraine, because all occupation neuroses are more prevalent among the neurotic and the sensitively organized.

Alger (57) says that there are three ocular conditions conceivably concerned with attacks of migraine: (1) Overuse of ciliary muscle in accommodation; (2) Conditions rendering binocular vision impossible without undue strain of extrinsic muscles; (3) The cerebral fatigue consequent on constant interpretation of distorted or unequal retinal images. The one great defect in the evidence of the relation between these conditions is the widespread

failure of ocular therapeutics to afford relief, even when applied by men whose reputations are of the highest. This may be due to two causes: First, that the ocular treatment is seldom as patient and painstaking as it should be; and, second, because there may be cases in which eyestrain is not the chief cause and perhaps not a cause at all.

At a meeting of the American Medical Association in 1908, Dr. Kenneth Bradford (9) said that the prime object of his paper was to bring before the Association the important connection between organic defects in the eye and that complex functional disorder known as migraine. Continuous relief, for a period of seven months, from attacks of migraine of increasing frequency of a most aggravated type has, in the authors own case, followed immediately on the detection and correction of a rather unusual refractive error.

Wallis (53) who also favors the reflex theory, cites the following cases of migraine patients with ocular defects who were relieved of the migraine symptoms by the correction of those ocular defects:

- (1) Man, aged 52, typical textbook symptoms of migraine; very slight mixed astigmatism and presbyopia. Complete relief by glasses.
- (2) Girl, aged 15, hemicrania and sickness, but no optical sensations. Hypermetropic astigmatism. Correcting lenses lessened greatly the severity and frequency of the headache, and entirely relieved the sickness and nausea.

- (3) Woman, aged 19, attacks of migraine replaced by nausea and momentary giddiness and slight sickness. Entire absence of headache or other phenomena. Father and grandmother affected by classical migraine. Myopic astigmatism and hyperphoria; complete relief by correcting these.

In regard to the scotoma of migraine, Edridge (23) says that the condition present in migraine is a central scotoma increasing from within outwards. The foveal region of the retina, which contains only cones, is sensitized from the peripheral portion containing rods, by the spread of the photo-chemical fluid over the ends of the cones. Any disturbance of the circulation in the eye preventing the flow of photo-chemical fluid to the fovea would thus produce a central scotoma increasing from within outwards.

3. The Central Theory.

Moebius (43) and Krafft-Ebing (35) were among the first to advocate the central theory as the cause of migraine, believing that the motor and sensory symptoms are due to irritation within the cerebral cortex. The headache of migraine has also been explained by the possibility of direct local or general pressure upon the dura mater such as might be caused by collections of cerebro-spinal fluid.

Gowers (27) is an advocate of the central theory, and he considers migraine as primarily a cellular disturbance of the central nervous system which produces, secondarily, the vaso-motor symptoms. He believes that some process elsewhere in the

brain affects the vasomotor centers, but that just which vessels or cells can be responsible for the strange mixture of release and excitatory phenomenon of migraine cannot be determined. He states that the prodroma is due to a crude disturbance of function, probably in the cerebral cortex, which ripples through the centre, leaving a state of inhibition which soon passes off. And, that all explanatory hypotheses are unsatisfactory, the most acceptable being the theory of local vasomotor spasm.

Levi (38) assumes the existence of a migraine center in the floor of the fourth ventricle. The trigeminal fibers which supply the dura may be represented there, and the hemi-crania would be due to a discharge from them. The discharge may spread to the neighboring nuclei and give rise to the various other symptoms: to the glosso-pharyngeal (nausea), vagus (vomiting and modification of pulse and respiration), to Deiters nucleus (vertigo), and to the vasomotor, salivary, urinary and ocular centers. The spread of the discharge may be limited, so that only some of these centers be affected. It may also spread to the facial nucleus, causing spasm or palsy of the face. This migraine center admitted, the attacks depend on the susceptibility of the instability of the center, and on direct excitation of it. The instability of the center is often hereditary, but may be acquired, as each attack makes the occurrence of subsequent ones easier. The direct excitation may be any emotional or visceral disturbance, but is generally an auto-intoxication. The attacks of migraine which occasionally

accompany the menstrual periods in women may be due to auto-intoxication of ovarian origin. Levi further suggests that an attack of migraine may be a defensive process, a method of getting rid of the toxic substance.

Hilpert (30) states that Stohr has recently shown that the nerves of the pia and of the pial sheaths around the vessels are derived from the carotid and vertebral plexuses and from branches from the third, sixth, ninth, tenth, eleventh and twelfth cranial nerves and that they end in small end-corpuscles. In view of this, the headaches become explainable from transudation in the pial sheaths producing a local effect, or from an acute increase in the cerebrospinal fluid which is not reabsorbed as quickly as it should be. In the same way this production of hydrocephalus would explain the vomiting as due to irritation of the ending of the vagus nerves in the pial sheaths. Hilpert (30) found thickening of glia and accumulation of corpora amylacea in the region of the lateral ventricles. In this particular case of his, necropsy showed no gross abnormalities. Microscopically, there was fatty degeneration in the entire cortex, affecting chiefly the fifth layer, especially in the temporal lobes. The glia cells contained much fat. Corpora amylacea in great number were found in the walls of the lateral ventricles, in the optic sheaths and in the cornu ammonis. They were present also in the occipital cortex.

Babonneix and David (4) claim that meningeal reactions play a part in the symptomatology of ordinary migraine, and that there is in migraine a hypertension of the cerebro-spinal fluid--

and that this explains the good results which lumbar puncture gives in some cases. They draw special attention to the aggravation of the pain of migraine by coughing or sneezing, either spontaneous or volitional. They think that at each shock of a cough or sneeze the cerebro-spinal fluid, in a state of momentary hypertension, disturbs the sensory trigeminus root, and so provokes a pain which is propagated to its meningeal terminations. They therefore regard the pain of migraine as due, not merely to a neuralgia, but to a true radiculalgia of the fifth nerve. And this radiculalgia is itself dependent on hypertension of the cerebro-spinal fluid, which is sometimes relieved almost instantaneously by lumbar puncture.

Mechanical obstructions to the cerebral ventricular system have been postulated. According to Grinker (28), the foremost of these theories considers a stenotic foramen of Monro, which, in becoming plugged by a hyperemic choroid plexus, causes a hydrocephalus. The increased intracranial pressure causes the cerebral symptoms and headache. When the pressure reaches a certain point within the ventricles, the plexus is dislodged and the cerebro-spinal fluid flow reestablished.

Also, according to Grinker (28), an angioneurotic increase in fluid secretion and an edema of the brain have been suggested. "Signs of increased intracranial pressure are minimal, however. The optic discs are not even hyperemic; there is no measurable increase of cerebrospinal fluid pressure during the headache. However, the vomiting and its occasional relief of the headache, the frequent slow pulse and the extreme head pain are very

suggestive of an intracranial factor in the production of the headaches. Intracranial and intraventricular pressures are simultaneously increased as a result of (a) increased secretion of lymph by the choroid plexus, (b) impairment of its reabsorption, (c) increase in arterial pressure or reflex dilation of cerebral vessels, (d) interference with venous outflow, (e) intracranial tumors. That all of these conditions can give rise to headache appears to be firmly established, the only question at issue being whether the effects are mediated by stretching of the dura or by direct stimulation of structures surrounding the ventricles."

According to E. Cutler (17), "The mechanical theory of headache so formulated is capable of explaining both the association of headache with local conditions and with more remote disorders of function. Since cerebro-spinal fluid secretion is affected by glandular hormones, a possible association of headache with various endocrine disturbances, including those affecting ovulation and menstruation is understandable. "With the demonstration by Weed and Hughson (31) that the volume of cerebro-spinal fluid and intracranial pressure are inversely related to the tonicity of the blood, the possibility that increased water retention and hypotonicity of the blood following intestinal stasis, constipation or renal affections may lead to increased intracranial pressure becomes plausible and particularly so as headache frequently disappears soon after great elimination of water either by free diuresis or purgation. The headache so frequently associated with great hypertension becomes explicable

on the grounds that increased arterial pressure per se increases brain volume by producing a greater blood content and perhaps also increases the secretion of cerebrospinal fluid by the choroid plexus. The common absence of headache in association with passive congestion of cardiac decompensation now becomes intelligible since the demonstration by Weed and Hughson that intracranial and venous pressures are not necessarily equal as was formerly supposed. While mechanical alterations of intracranial and ventricular pressures thus account logically for the frequent association between headache and many local as well as remote disorders, it cannot be claimed that this mechanism accounts for all forms of headache."

4. The Allergic Theory.

Storm van Leewen and Zeydner (49) state that during the past few years it has become clear that illnesses like asthma, hay-fever, urticaria, etc., have in most instances to be considered as allergic, which means that they are due to a hypersensitiveness to substances which are innocuous for normal people. "An attempt has been made to demonstrate that this condition is an anaphylactic one, but this view, as has been emphasized by Coca, Cooke, and others, must be abandoned. The related condition may be related to anaphylaxis, but it is not a true anaphylactic phenomena, such as occurs in animal experiments." The authors state that it is known that in allergic conditions, there is usually a hypersensitiveness to several agents; and also, that such patients are apt to be of a nervous disposition, so that there is considered to exist a hyperexcitability of the

sympathetic system. However, these authors approach the problem from this angle: viz., that "generally speaking, allergic conditions are, ----- due to a hyperexcitability of smooth musculature in the lung (or other organ). This hyperexcitability is due to a substance present in the blood of these patients, a substance which has the property of stimulating smooth muscle." And, the authors carried out experiments to test this hypothesis, and briefly, their results were as follows: Blood was drawn from 23 men (10 normals, 9 asthmatics, 2 intense urticaria, 1 epileptic, and 1 migraine,) and the blood treated in such a manner that the substance which is always present in normal serum which will stimulate smooth muscle, was removed or at least made inactive. This having been done, it was found that the extracts of all the normals showed no action at all on the gut, if certain doses were used. The extract of the blood of one very light asthmatic was also negative, but "in all the other cases of asthma and in the cases of urticaria and migraine, the blood extract contained a substance which had a very definite action on the smooth muscle of the gut." Roughly calculated, they found that one liter of blood contained a quantity of the unknown poison which had an action similar to 2-5 mg. of pilocarpine. These poisons were found in the blood of persons during periods of apparently good health, not during an attack of the disease, and therefore they look upon this as an indication of a "pathological state", or an "allergic disposition." They state that although these findings are of considerable interest, they by no means solve the question, but only open up a new field for investigation.

Joseph S. Diamond (19) favored the allergic theory of the cause of migraine, (although he realized that there were types of migraine other than those produced by allergic factors,) and wrote quite an exhaustive paper in support of this theory. The following paragraphs are quoted from that paper:

"From a study of the clinical picture, familial background, causation, and therapeutic response, we may recognize the following groups:

1. True migraine produced by noxious agents such as (a) allergic or (b) hepatic and metabolic factors.
2. Endocrine migraine due to hormonal dysfunction, comprising the menstrual and other types of gonadal headaches.
3. Symptomatic migraine including all headaches which are secondary to well established physical causes.

"There seems to be good reason to regard migraine as an allergic manifestation responding with cerebral and meningeal vascular crisis as a hypersensitive reaction to certain foods. The analogy can be drawn from the paroxysmal nature of the attacks, which come in individuals in apparently good health, resembling in character the exudative crises, such as asthma, angioneurotic edema, and urticaria, also vascular crises such as angina pectoris, intermittent claudication, abdominal angina, paroxysmal tachycardia, and a group of abdominal symptoms which Cooke classed under gastro-intestinal allergy.

"The hereditary nature of migraine is another point of analogy. When a careful history is taken, one finds other forms of allergy in different members of the same family. In a series

of thirty cases studied by me when such careful questioning was undertaken, over fifty per cent showed the presence of either urticaria, vasomotor rhinitis, andioneurotic edema, itching of the skin, gastro-intestinal attacks, etc. Eosinophilia from three per cent to as high as ten per cent was found in thirty-five per cent of the cases.

"When we come to apply cutaneous food tests we meet with disappointment. With the exception of solitary instances, these tests were uniformly negative. Even in the hands of the most sanguine workers in this field, such as Balyeat and Rowe, the tests are negative. We cannot deny, however, certain experiences where the withdrawal of certain foods will definitely give relief from the attacks. I can cite from my own personal observation a number of instances, one of a pious gentleman who lived throughout the week the life of an ascetic, eating sparingly of vegetables, milk and bread, and who for years would develop on the Sabbath day the most violent attacks of migraine. It was discovered that on the Sabbath eve he would permit himself a more substantial diet consisting of meats and fish. The withdrawal of the meat gave him prompt relief.

"In other instances the outbreak followed the ingestion of smoked tongue or salmon and in a few, after the inhalation of tobacco smoke. The withdrawal of the offending substances brought about relief. Yet in all these instances the cutaneous reactions for the respective foods and tobacco were negative.

In the discussion of cutaneous reactions, it is maintained by immunologists that they are positive only where the clinical

manifestations are immediate, say within an hour after eating, but when they are delayed for several hours or days, the cutaneous reactions are always negative."

Joseph L. Miller (41) says that the accidental discovery that epilepsy and migraine are relieved by the intravenous use of various foreign proteins and by peptone has led to the view that both may be anaphylactic in character, and there is considerable evidence to support this view. Asthma, and hay-fever, recognized sensitization diseases, are both definitely hereditary. Heredity is evidenced in 90 per cent of cases of migraine and 20 per cent of cases of epilepsy. Their frequent temporary, and occasional permanent, disappearance after severe acute infection might be accounted for by desensitization. Frequently, bronchial asthma disappears during pregnancy; attacks of migraine, as a rule, are less frequent, or entirely absent, during pregnancy; Anaphylactic shock in animals is always associated with eosinophilia, and Gansler (26) reports eosinophilia of from 5 to 15 per cent in 74 per cent of migraines. Excitement or worry is an important factor in exciting migraine or epileptic seizures and we have an analogy in nervous asthma. We know little of the nature of the sensitizing agent--perhaps as in asthma a great variety of proteins may be responsible.

Balyeat (5) thinks that heredity is one of the most important factors in the production of migraine as is shown by a positive family history of allergy in 85.4 per cent and a family history of migraine in 45.4 per cent in the fifty-five cases of migraine studied. The exciting factor is always a

specific sensitivity to one or more foreign proteins, and multiple sensitivity is the rule. Physical fatigue, mental fatigue, depressed states, thyroid dysfunction, genito-sexual causes, toxic states and disturbance of the special senses are predisposing factors. Five cases are cited as illustrations of the aforementioned points. In one third of the cases the onset occurred in the first decade, and 12.7 per cent symptoms persisted until the sixth decade. Balyeat (5) also demonstrates the close relationship between conditions due to sensitivity to food, such as asthma, cutaneous visceral reactions and the so called cyclic vomiting, and migraine. He disagrees with the usual opinion that migraine is due to a sudden localized vasomotor spasm of the vessels of the cerebral cortex. He offers the premise that it is a condition of vasomotor dilatation, and reports that about 15 per cent of all of his patients with migraine obtained relief by the use of ephedrine.

The following is quoted from Moloney (40) in regard to the allergic factor in migraine: "It has been suspected that the substratum underlying the "volcanism" of migraine is identical with the process responsible for epilepsy and such allergic phenomena as asthma, hay-fever and urticaria, and that the respective clinical manifestations are but regional displays of one and the same mechanism. Further, it has been intimated, that this mechanism is hereditary, being transmitted according to the principles of Weismann after the theory of Mendel. But it is known to be more than hereditary. It is an intrinsic condition, and, like gun-powder, requires a detonator to bring

about an explosion. These detonating substances are countless, and Gordon, in speaking of the spark that fires the load, facetiously observed, "Who frowed dat brick?". Pollens, dander, bacterial proteins, biliary infection, catabolites and colonic residue have been impugned in turn."

The authors summary and conclusions are:

1. A submerged intrinsic physiopathic mechanism is responsible for allergy and for migraine.
2. This mechanism is similar for both conditions, the clinical manifestations being regional expressions of the same process.
3. This mechanism is hereditary. Heredity is only partially selective in its regional expression; nonallergic persons with migraine have a higher percentage of allergy in their family history than do nonallergic persons who do not have migraine; likewise, nonmigrainous allergic persons show a higher percentage of migraine in their family history than do nonmigrainous persons without allergy.
4. Recent work by other investigators and my own studies on epilepsy would tend to preclude the possibility that epilepsy is due to the same mechanism that causes migraine and allergy.

The author's observations were made upon 428 unselected cases, in which there were 36 of migraine, 38 of psychogenic headache (used as controls) 62 of allergy and 68 nonallergic patients.

Cecil (14) writes that patients with migraine frequently

have periods of relative immunity, during which nerve strain, that would ordinarily bring on an attack, is without effect. These might be considered refractory periods corresponding to an anti-anaphylactic state, and they emphasize the points of similarity between asthma, which is certainly anaphylactic, and migraine. In each, the attacks are periodic, nervous influences are important in precipitating an attack, the disturbance frequently disappears temporarily after some prolonged infection, and pregnancy sometimes exerts a favorable influence. A certain kind of food has been known to institute an attack in both conditions. Migraine as well as asthma is often accompanied by eosinophilia. These points at most suggest by analogy that migraine is a sensitization disease. Brown (12) believes that in migraine the condition of the gastro-intestinal tract and the character of the diet play at least a secondary or contributory role in producing the explosive phenomena. He divides cases of migraine into four groups: (1) Those associated with intake of more carbohydrate than can be utilized; (2) those associated with the intake of animal food, either in excess or of a type which sets up a specific reaction; (3) those few associated with true intestinal toxemia caused by the decomposition products of protein digestion which are possibly related to histamine; and (4) those associated with metabolic abnormalities which require complete avoidance of purine-containing foods. Timme (50) believes that there are two classes of food which invariably precipitate attacks of migraine in predisposed individuals; i. e., substances rich in iodine, such as fish,

oysters, clams, and occasionally even spinach; and carbohydrates in excess.

5. The Toxic-Metabolic Theory.

Toxic-metabolic disorders, acting reflexly, are considered by a number of writers to be the underlying cause of migraine. This theory of the causation of migraine involves all of the common exogenous and endogenous poisons. The various acute and chronic infectious diseases have also been implicated, particularly the so-called gouty diathesis.

Adie (1) states, "It is not unlikely that circulating toxins from whatever source, toxins elaborated during catamenia, or from the gastro-intestinal tract, may influence the cerebral blood vessels to produce changes, either dilatation or contraction, which lead to pain. Pain from functional vascular changes probably is not meningeal in origin, since that structure is relatively insensitive. Blood vessel pain itself may be an actual possibility, not transmitted over the cervical sympathetic trunk, since that contains no afferent fibers from the head, but by way of branches of the trigeminal nerve. Therefore, interference with the cervical sympathetic is not rational therapy, for it could probably not even relieve the vasomotor changes, much less the pain, as the blood vessels are capable of contraction from local stimulation by catabolites or from generally circulating toxins."

Diamond (19) says that the second important consideration in the etiology of true migraine (the first being allergy, as cited earlier in this paper), is hepatic dysfunction causing

toxic or metabolic disturbances due to a deficient intermediary metabolism of the liver. In a series of 35 cases of outspoken cerebral and abdominal migraine which were collected up to 1926 and previously reported, he found in 19 cases, over fifty per cent marked evidences of liver insufficiency according to the van den Bergh and urobilinogen tests. In his present series of 30 cases, the percentage of hepatic insufficiency approximated the previous findings, the van den Bergh always being higher in the severer types of migraine in those cases associated with gastric upsets, and highest in the abdominal type of migraine. Constipation is a so very marked and is an outstanding complaint. In the patients of this series the feces were found to be composed of small dry scybala which were retained in the transverse colon and descending colon for days. The migraine attack invariably developed when a dietary indiscretion of the offending food took place during the period of constipation. This brings up the question of an intestinal toxemia, and the relation it bears to impaired liver function. If prompt and effective catharsis were induced, the attack would be shortened or would be aborted. In this connection, the author says that he may safely say that there exists constitutional or hereditary metabolic factors which cause interference in the normal detoxication function of the liver of the products of decomposition in the intestinal canal. This inherent hepatic deficiency may also apply to the inability to synthesize the amino bodies of certain food proteins, which when allowed to escape into the general circulation, liberate the paroxysmal attack of migraine.

The author then proceeds to say that it is here that the allergy and hepatic dysfunction may be finally linked together, and that when more light is thrown upon the subject of allergy, it may be found that the liver, when functionally disturbed, especially relating to its detoxicating process, may play an important role in at least one form of allergy, through the liberation into the general circulation of the intermediary products of protein metabolism which give rise to the well known phenomena of allergy. These chemical derivatives may be the real allergen which are claimed by immunologists to be liberated into the body hours after the oral introduction of the mother protein.

Also, McClure and Huntsinger (39) write as follows regarding the role of liver dysfunction and the production of toxins as an important factor in the production of attacks of migraine: "A prominent feature of the findings outlined in the protocol is the frequency of the evidence of pathological involvement of the gall bladder. Such involvement was demonstrated upon operation in only two patients; while the evidence of it in the remaining patients was obtained from X-Ray films. For this purpose the well known Graham procedure of Whitaker was used. It is recognized that apparent abnormalities found in the film, after the use of this procedure, do not furnish unquestionably conclusive proof of the gall bladder disease. But the percentage of abnormal findings occurring in this series of patients is too great to be attributed as due solely to errors inherent in the method. Additional evidence of the existence of gall bladder disease was the complaint of epigastric pain simulating gall

stone colic in four of the patients. Another striking feature portrayed by the protocol is that of disturbance in the state of liver function. This was determined by analysis of duodenal bile, according to methods previously published. By the use of these methods the functional activity of the liver was studied in 20 patients and was demonstrably abnormal in 15 of these. In addition, study of the intermediary metabolism of fats has yielded results suggestive of disturbed hepatic function in patients whose duodenal bile was not found to be abnormal. Therefore, the findings show that evidences of functional hepatic disturbance and pathologic gall bladder involvement were so frequent as to suggest that these conditions may be considered as part of the symptomatology of migraine."

In his summary the author states that "Evidences of intoxication were found which it is suggested participate in the production of migrainous symptoms. These evidences are the frequency of the presence of disturbed liver function and the less often occurring demonstration of protein sensitization."

In regard to duodenal ileus being the cause or at least one of the factors in the production of the supposed toxins present in the migrainous patient, and producing his attack, McClure and Huntsinger (39) further state: So-called duodenal ileus is an x-ray diagnosis. It is made when anti-peristalsis accompanies stoppage of barium in the region of the junction of the second and third portions of the duodenum. Such phenomena are usually produced by one of two conditions. One is true organic obstruction of the duodenum, and the other hyper-sensitiv-

ity of the bowel. In the presence of the latter, anti-peristalsis may be more apparent than real because the forceful contraction of the gut on a central bolus of barium causes a portion of it to progress proximally as well as distally. The temporary sojourn of barium in that particular region of the duodenum is a normal phenomena ordinarily explained on a well known anatomical basis. The constitution of an abnormality by difference in time is not always easy to establish. In any event, these phenomena are not uncommonly demonstrable in migrainous subjects. They are also found in the presence of a variety of conditions which render the gastro-intestinal tract hyper-sensitive to stimuli. Therefore, in migrainous subjects the gastro-intestinal tract is frequently hypersensitive to stimuli. Because of this hyper-sensitivity, the occurrence of so-called duodenal ileus in migrainous patients is to be anticipated. On the basis of these findings, and in the absence of organic obstruction, it is concluded that so-called duodenal ileus is a result of an accompanying hypersensitive gastro-intestinal tract, rather than a cause of migraine." Also, "Liver functional disturbance was demonstrated in 90 per cent of the 72 patients examined. Relief from, or improvement in, the headache was obtained in 79 per cent of 29 patients by treating the disturbed liver functional state. Furthermore, abnormalities in lipid metabolism occur in migraine which are comparable to those demonstrated in affections of the liver. These observations indicate that the liver plays an important role in the production of migrainous symptoms. The occurrence

of positive cutaneous protein reactions, the frequent incidence of demonstrable liver functional disturbance, and the presence of abnormal lipid metabolism in migraine are definite pathologic findings. Although their etiological significance remains unsettled, their occurrence establishes the fact that migraine is not merely a functional brain disorder. The fact that food proteins may act as substances toxic to certain patients, and that toxic substances do disturb hepatic function, suggest that migraine is frequently the result of a toxemia."

Below are listed the metabolic and biochemical investigations of the migrainous patient, which, as Riley (47) states "leave much to be desired as to completeness and comprehensiveness."

(a) Urine.-- Bioglio (7) says that in every form of hemicrania there are alterations in the elimination of the principal organic and inorganic elements of urine. The nitrogen metabolism is slightly retarded in the hemicranias during the intervals between the attacks; the amount of chlorides, total sulphuric acid, and earthy phosphates is below the normal; elimination of phosphoric acid is normal. During the attack the nitrogen elimination is constantly accelerated; the other elements may or may not vary. There is a marked difference between the epileptic and the hemicranic with regard to metabolism. (b) Blood.--McClure and Huntsinger (39) give the following summary and conclusions of the character of blood lipids in hepatic disorders, including migraine: 1. Hyperlipemia, abnormally low iodine numbers for cholesterol and unusually high ones for fatty acids of the blood during the fasting state are indications of disturbances in lipid

metabolism in patients with the diseases studied. (10 patients with migraine observed). 2. As shown by changes in the iodine numbers and in the concentrations, ingested food stuffs influenced the character of the lipids of the blood of the patients studied. The influence on the character of the lipids was usually comparable after all types of test meals, and in all conditions studied. Qualitative and quantitative differences, however, were frequent and occasionally strikingly great. 3. The gross changes in the lipids of the blood of patients, demonstrated after the ingestion of food, are interpreted as the result of their mobilization from the tissues of the body. The character of the iodine numbers of the lipids so mobilized suggests that they either were of abnormal form or represented an abnormal reaction of the tissues to stimulation. 4. The observations suggest that the cholesterol of the blood of the patients studied differs in chemical constitution from that of normal subjects. (c) Spinal Fluid.-- Kerppola (34) examined the spinal fluid of five patients during an attack and his findings are so nearly identical with those considered as normal that no extended comment is necessary. The pressure is within normal limits in all the cases. The albumin is somewhat high in the last case but there is no information as to the number of cells or the possible presence of small quantities of blood. The figures for sodium chloride and sugar are quite normal.

(d) Basal Metabolic Rate.--The basal metabolic rate was investigated by Moehlig (42) in a group of 51 migrainous patients. He found that 40 per cent of the females gave a rate which was on

the plus side of the scale, averaging plus nine per cent. 60 per cent of the group gave negative readings averaging negative 10.9 per cent. Although these figures do not present any striking deviation as compared with other groups of patients, even as they stand they are open to question, since the majority of patients in whom the tests were made lived in a goiter zone.

(e) Blood Pressure.-- The blood pressure was investigated by Moehlig (42) in a group of 100 migrainous patients, of whom 69 were females and 31 were males. He reported that the average blood pressure in the females was 129/80 mm. of mercury, the extremes being 90/48 and 190/40, and in the males 128/80, the extremes being 90/60 and 210/130. The blood pressure was investigated also by Kerppola (34), who found that it bore no significant relation to migraine. During the attack the blood pressure might rise about 20 to 30 mm. of mercury.

6. The Hypophyseal Theory.

Timme (50) is of the opinion that local disturbance in the size and activity of the pituitary is a causative factor in the production of certain cases of migraine. He feels that migraine is a symptom of an underlying condition and is often associated with eye-strain or to slight disturbances in refraction or to muscle imbalance. One type is due to compensatory hyperactivity of the pituitary body and an enlargement of the pituitary gland.

Dickerson (20) found in six cases of migraine varied evidence of increased bone formation in the region of the sella turcica. He believed that when evidence was found of this abnormal calcification, the diaphragm sellae was more strongly developed

than was normal. In two instances there was radiologic evidence of abnormal interclinoid ossification in a mother and daughter.

Touraine and Draper (51) made a constitutional study of the migrainous patient, and they state that usually the face of a migrainous individual appears to be slightly oversized in relation to the rest of the body. The increase is evenly distributed in all diameters, but there is perhaps greater emphasis on the transverse diameter of the upper facial zone; namely, between the zygomata. The eyes are set widely apart, and this arrangement increases the impression of unusual breadth in this area. They come to the conclusion that the facial characteristics of the migrainous are clearly those which are found in exaggerated form in acromegaly, and state that it is interesting that the acromegaloid trend is not reflected in other parts of the body. Indeed, the hands of these patients are narrower, and more pointed than is usual in the acromegalic. They suggest more the hands of the Froelich type. Furthermore, in this connection, hyper-extensibility of the fingers is commonly noted. Their conclusion is that from the foregoing observations it appears that the morphological panel of the migrainous constitution contributes in some degree to the whole picture. Especially the conformation of the skull and facial bones is reminiscent of acromegalic forms and so draws attention to the special emphasis of pituitary influence on the growth of the skull in the migrainous.

Edward F. Hartung (29) writes that, "The very nature of the malady stamps it as deep set constitutional disorder. Constipation, or eyestrain, or a retroverted uterus may be the

immediate exciting cause of a particular migrainous attack, but this is not the fundamental explanation. For example, a patient with migraine may have an attack due to constipation at one time, emotional stress at another, or carbohydrate excess at another time. In short, removing the immediate exciting cause will almost never entirely effect a cure. As to the theories of migraine which seek a more fundamental explanation, they must have merely an historical interest. Only two need our attention now. One is that migraine is a manifestation of a vasomotor disorder of the cerebral circulation, either transitory hyperemia, or anemia, or both alternating. The other theory, to which we ourselves are inclined is that migraine is a pituitary disorder, and proof is gradually accumulating to place this idea on firmer ground. Due to an extra demand on the organism, the pituitary is called upon for an increased output of its secretion and with the acceleration of its activity becomes engorged and enlarges. Being inclosed in an inexpandible bony cavity, the sella turcica, its enlargement causes pain. The outlet to the sella is superiorly, and here the optic chiasm is situated. Pressure on the chiasm could anatomically account for the visual symptoms, the scotomas, and hemianopsias so often seen with migraine."

Charles (15) states that none of the great number of hypotheses advanced to explain the production of the symptoms of migraine are altogether satisfactory, and his paper is written to support the contention that all the clinical features of the disease may be explained satisfactorily on the assumption that

they are due to periodical enlargement, probably to a pathological degree, of the pituitary gland. "According to this hypothesis, some of the symptoms are to be attributed to direct pressure effects on neighboring structures, the remainder to the effects of a somewhat sudden increase in the absorption of the normal secretion of the posterior lobe of this gland." The author states that there is a physiological variation in the size of the pituitary gland, and proceeds to say that in pregnancy it is known that the gland becomes hypertrophied to two or three times its normal size, this enlargement occurring in the anterior, or glandular portion, (there is considerable involution of the of the gland after termination of pregnancy). He then proceeds to the assumption that, since this enlargement occurs during pregnancy, (it is known that there is an important physiological relationship between the pituitary gland and the generative organs), it is reasonable to assume that an enlargement occurs, (though to perhaps to a lesser degree) during menstruation, or other sexual disturbances, and perhaps at other times. He then cites the known fact that migraine is much more common in females, and also is much more common during menstruation than at other times; and in addition, migraine frequently lessens or disappears entirely following the menopause. That is, there is a physiological intermittent enlargement of the anterior portion of the pituitary gland, due probably to some chemical stimulus, or hormone, (possibly connected with the reproductive organs).

Hartung (29) next proceeds to explain the mechanism of the production of the symptoms of migraine by this enlargement of

the anterior pituitary gland. (a)--Headache. Due to swelling, probably to an increase in intracranial pressure, and possibly also to vascular changes, constriction or dilatation. (The distribution of the pain corresponds to irritation of the upper branch of the fifth nerve--exactly the branch which would be pressed upon by an enlarged pituitary. The subjective pain, may of course, be felt by radiation beyond the area of distribution of the nerve primarily irritated.) (b)--Nausea and Vomiting. Due probably to increased intracranial pressure. (c) --Disturbances of Vision (mainly hemianopia). Permanent hemianopia is known to occur as a result of pituitary tumor. Transient hemianopia may occur secondarily to the swelling of the pituitary in pregnancy. He therefore assumes that transient enlargement of the gland during migraine, produces irritation of the optic tracts secondary to pressure. (d)--Vasomotor Phenomena. Due to the fixity of the anterior and posterior boundaries of the sella turcica, a compression of the posterior lobe, resulting in an expression of an abnormal quantity of secretion from the posterior lobe into the third ventricle, causing a rise in blood pressure or vasoconstrictor effects, (hence the initial pallor and feeling of chilliness) occurs due to this assumed enlargement of the anterior portion. He explains the occurrence of uni-lateral sympathetic nerve fibers (cavernous plexus) surrounding the internal carotid, which is in close relation to the pituitary. These sympathetic nerve fibers communicate, via the superior cervical ganglion and nervi molles, with the sympathetic fibers on the branches of the external carotid, and in

this way accounts for such signs as pallor or blushing limited to one side of the face.

Finally, Hartung (29) says: "We have x-rayed a large series of sella turcicas in these cases. The x-ray technique of taking the sella is variable, the apparent size of the sella being dependent almost entirely on slight variations of focal distances and angles. Besides no mathematical method of comparing the size of sellas as they present themselves in x-rays has been worked out. However, it is our distinct impression that the sellas in migraine patients are predominantly small, giving little room for expansion except upward. When an extra demand is made on the pituitary for an increased output of its secretion it has little room for expansion in a small sella. It is true that while pregnant women are apt to be free from attacks of migraine, their pituitaries are definitely larger in size and weight. But this enlargement is a slow process in pregnancy and may not give symptoms, just as slow-growing cerebral tumors frequently do not cause disorders untill decidedly large."

7. The Endocrine Theory.

A large number of authors believe that disordered function of the hypophysis is responsible for the symptoms of migraine, not through mechanical effects, such as the periodic hypophyseal swelling with pressure upon neighboring structures, but by a disfunction of the gland itself, producing a change in its own secretion or its control over other incretory glands. However, it is difficult to accurately differentiate or to draw a very definite line between the two theories; i.e., disfunction or

overactivity of the pituitary gland as a cause of migraine, and the mechanical effects of a pathological enlargement of the gland producing the symptoms of migraine, because overactivity results in enlargement with mechanical effects. However, the two theories are considered separately here, as is done by Riley (47).

Hartung (29), who does not differentiate between the two theories, writes: "Many elements of the migraine constitution readily suggest an endocrine association, for example, the onset of the malady around puberty, and its cessation around the climacteric. Also the fact that women, while they may have an attack at any time, frequently have one around the menstrual period. Another interesting observation is that women who become pregnant are very apt to be practically free from attacks for the entire nine months, and after parturition the attacks will recur. This is not an invariable observation, but it is common enough to be distinctly significant. Many factors in the symptom complex and the makeup of the patient suggest a pituitary disfunction. Such, for example, are the sympathetic nervous suppression or atonia exhibited by the low blood pressure that these patients usually present, the general asthenia, low fatigue threshold, extreme reaction from loss of sleep, and susceptibility to carbohydrates in excess. During the attack there is apt to be slight diarrhea, irritable bladder, a still lower blood pressure, a slow pulse and pallor. All these suggest a vegetative nervous system disorder, a suppression of the sympathetic tone, and more fundamentally suggest to us a dispi-

tuitarism with hypo-pituitarism predominating. It is to be recalled that the hypophysis, in association with the thyroid and the suprarenals, stimulates the sympathetics, a suppression of its activity leading to vagotonia. An attack of migraine would be considered an attempt on the part of the hypophysis to assist the control of sympathetic system when it becomes too attenuated."

Riley, Brickner, and Kurzrok (47-A) made hormonal studies daily over a prolonged period of the urine of thirteen patients, 11 female and 2 male, suffering from migraine. The period of observation has in each instance included a typical attack. In the urine of female patients, the studies have embraced the quantitative estimation of female sex hormone, and the identification of prolan. In the urine of male patients only the identification of prolan was included. No distinction was made between prolan A and prolan B.

Results: (1) Theelin was occasionally present in the urine of all but one of the women of menstrual age, and in this one the menopause was imminent. In the urine of one woman who had passed a natural menopause, theelin was absent, as was the case also in that of another woman in whom the menopause had been induced by operation. In all of the cases in which theelin was demonstrated in the urine, the hormone was absent from the urine sporadically; when present the amount of theelin rarely exceeded 5 rat units per liter. Only exceptionally did the quantity of hormone reach from 10 to 20 rat units, which is considered the normal amount for women within the menstrual age.

(2) No demonstrable relationship was determined between variations in the excretion of theelin and the occurrence of headache.

(3) In all cases prolan was excreted. In the urine of the two women past the menopause and of the one approaching it prolan was present almost daily in large quantities; in the remaining eleven cases the hormone was demonstrated in the urine intermittently and in varying amounts.

(4) In all the patients, 29 individual headaches occurred. Headaches that continued over consecutive days were considered, for purposes of tabulation, as constituting a single attack. In two patients the headaches were so continuous as to constitute a state of migraine. Not being separable into single headaches, this prolonged condition could not be included in the number given (29). 20 of the 29 headaches were preceded or accompanied by the appearance of prolan in the urine. The number of days by which the appearance of prolan antedated the headache was determined by counting from the first day of the appearance of the hormone to the beginning of the headache.

"It should be noted that frequently, and particularly when prolan first appeared several days in advance of the headache, its excretion continued for a number of days, terminating just before or concomitantly with the appearance of the headache. In the urine of one patient, prolan appeared on each of three consecutive days antedating the headache and disappeared with the occurrence of the headache. In the urine of another patient on one occasion prolan was demonstrated four days before

the headache, but continued to appear for three of the four days. In another instance, the appearance of prolactin in the urine preceded the headache by an interval of six days, and the hormone continued to occur in the urine on each of the six days, failing to appear only on the day of the headache. In four instances, the continuous excretion of prolactin extended through at least a part of the period of the headache. In one case the prolactin appeared in the urine for two days, was absent for one day, and recurred coincidentally with the occurrence of the headache. The incidence of headache and the excretion of prolactin limited to a single day coincided in only two instances. The interval by which the one antedated the other was in seven instances one day; in four, two days; in five, three days; in one, four days, and in one, six days. In the two patients presenting a state of migraine the excretion of prolactin was practically uninterrupted. There was, therefore, a continuous relationship between the appearance of prolactin in the urine and the occurrence of headache. In one patient, a practically continuous excretion of prolactin took place. In this patient it was therefore impossible to relate the headaches to any particular day when prolactin was excreted.

(5) In nine of the twenty-nine headaches no prolactin-headache relationship was demonstrated. In seven of the nine headaches, however, the determination of an exact relationship between the appearance of prolactin and the occurrence of headache was rendered impossible by the absence of specimens of urine. In the remaining two of the nine, the requisite number of specimens was

obtained, but the headache occurred without the antecedent appearance of prolan.

(6) Occasionally prolan appeared without the subsequent development of headache. Of the three patients showing almost daily excretion of prolan, one failed to have a headache on only one day; another was free from headache on only an occasional day, but the third, as stated, was free from headache during the major part of the time of observation. In only three of the remaining eight patients in whose urine prolan appeared intermittently did a headache fail to follow the excretion of the hormone.

(7) Of the eight women of menstrual age, seven had attacks with menstruation. The relationship between menstruation, headache and the excretion of prolan could not be shown to differ from the headache-prolan relationship occurring at other times.

(8) Nine female patients received injections of 2 cc. of the hormone occurring in the urine of pregnant women, and seven presented an attack of migraine within from four to twelve hours. The attack was either mild or severe but always presented the characteristics which were typical for the individual patient.

"Only two men were studied during the period covered by this preliminary investigation. One man had six and the other nine headaches. In the patient with six attacks, the specimens of urine obtained preceding one headache were lost; all of the other attacks were associated with the excretion of prolan

within a period not exceeding three days. In the other male patient, who had nine headaches, the specimens obtained preceding one attack were lost. Of the remaining eight attacks, only four were associated with the excretion of prolans".

"The hormone occurring in the urine of pregnant woman was administered twice to the patient with six attacks, the injections being separated by an interval of six days, with the development of a mild headache three days after the first injection, but with no headache subsequent to the second injection."

In a discussion following the reading of the paper of Riley, Brickner, and Kurzrok (quoted above), Walter Timme (50) said; "It is unfortunate that one cannot distinguish between prolans A and B at present, because each acts contrary to the other; there is doubt as to which of the two is meant. I think that an issue which might be clear is thereby confused. While one of the two prolans may produce headache, the other may alleviate it."

"Dr. Brickner was careful to say that there is some connection between the prolans and the headache; I agree with him. I do not think that the connection is causal for the reason that investigators have considered that the attack of migraine is limited to the headache alone. The headache is only one part of an attack, which can be divided into three stages. The first stage lasts for from half a day to three days; during this stage there is no headache, and the patient has a feeling of well-being. Then follows the headache, which also lasts for an indefinite period--from half a day to

three days. In the third or receding stage, there is relaxation of all functions, with a feeling of exhaustion that lasts a day or two. This would account for the fact that prolan appears in the urine a day or two before the headache begins. It appears with the initial enlargement of the anterior pituitary gland. No headache occurs as yet because the pressure has not increased within the sella. When the increase of pressure occurs, the headache begins. Prolan is not a product of the headache, but of the overactive anterior lobe of the pituitary gland. When studies are made, it will be found that a pituitary hormone is also released at the time of the headache. Before the headache the blood pressure is usually very low. A demand is made on the pituitary gland for an increased production of pituitary hormone; then comes the rise in pressure. At the beginning of the rise of pressure, before the headache starts, there is an increase of pituitary hormone in the blood; this increases for a time and then diminishes. Prolan will produce a headache on injection; pituitrin administered in a sufficient dose will cause a severe headache within from a half to one day, and so will some other products of the pituitary gland.

"Other glands are implicated. For instance when insulin is given in too great a dose and therefore produces shock, the first stage of recovery is accompanied by severe migraine in patients who suffer from migraine. Certain hepatic disturbances are accompanied by severe migraine in those predisposed to these headaches. In attacks of migraine there is disturbance in the interchange of water. Just previous to an attack

there is excreted only a small amount of urine, the cessation of the attack is ushered in by a large output of urine.

"In migraine the pituitary gland is not necessarily diseased; it is endeavoring to perform a purposeful act, to overcome disturbance elsewhere. If a similar capsule enclosed the suprarenal gland or the ovary there would occur similar physical signs from enlargement of these glands.

It was not stated whether the sella turcica was small or showed erosion or faceting in the patients reported. In patients with migraine the pituitary fossa shows the results of pressure. I wish to stress this disturbance of the pituitary fossa, and agree with Dr. Brickner and his associates that the precipitating cause is an abnormality in the sella or in the hypophysis. I do not agree that the factor of inheritance is sex-linked, with respect to the ovary, in its connection with the anterior lobe of the pituitary gland. I think that the unit of inheritance is the size of the sella turcica."

Philip E. Smith (48) also had some comment to add, following the reading of the above quoted paper of Riley, Brickner, and Kurzrok. He said, "The factual findings reported are of great interest. They point to one more condition in which prolan in the urine does not indicate pregnancy. Dr. Kurzrok's long experience places the facts beyond question. I wish to discuss briefly the suggestion that the pituitary gland is one cause in the production of these headaches. This generalization assumes that prolan is identical with the secretory product of the pituitary gland. Otherwise no such generalization

could be made. Dr. Kurzrok stated that some work had indicated that prolactin is not identical with the secretion of the anterior lobe of the hypophysis. This is correct and is important in regard to speculations on the causative role of the pituitary gland in migraine. To be sure, in Europe it is still generally assumed that prolactin is identical with the pituitary secretion. In this country, however, there is a growing mass of evidence which indicates that prolactin and anterior pituitary extracts are not identical. Where prolactin is formed is still a question. From the evidence given in this paper I should be inclined not to speculate on the pituitary gland as a causative factor in migraine. I find that it gives me less headache later if I do not generalize too much in print. To secure evidence of a hormonal nature which demonstrates that overactivity of the pituitary gland is a causative factor in migraine, there must be found in the blood of these people a substance which is identical physiologically with an active principle of the pituitary gland. The facts presented are of great interest, but conclusions drawn from them are apt to be premature."

Dr. Brickner's reply to the comment on his paper by Timme and by Smith was as follows: "Concerning the size of the sella radiographically and the question whether it was smaller than usual or malshaped, each patient was examined by stereoradiographs with this possibility in mind. In these cases no abnormalities of the sella were observed; there were no calcifications or other changes in the ligaments or dura around the sella.

" ----- . We do say and believe that there is evidence suggesting that some pituitary abnormality is related to these attacks. We do not know that this relationship is anatomic. I outlined the mechanical theory in full, but perhaps I was not clear enough in showing that we did not necessarily adhere to that theory. We thought it best to outline the various suggestions and thoughts of others which related the gland to the attacks, but we do not stand by any of them; our work is not related to them, and we do not believe that our results indicate, one way or the other, what the anatomic relation of the pituitary gland is to the attacks.

"As to Dr. Smith's comments, I think that we should make ourselves clear. The view which we have tentatively developed as a result of this work is: The evidence indicates that prolactin as it appears in the urine and therefore probably in the blood is related in some way to the incidence of each attack of migraine. We have thought that this is an indication, but an indication only, that the pituitary gland may be connected with the attack. Naturally, Dr. Kurzrok in particular, is cognizant of the current evidence that prolactin is not identical with the product of pituitary function. We shall depend on the studies of Dr. Smith and others for comprehension of the relations between prolactin and the pituitary gland and we shall continue to follow his lead."

SUMMARY

There seems to be little question at the present time that the tendency to the occurrence of migraine is transmitted from parent to offspring much in the same manner as other Mendelian characteristics, all writers (with few exceptions) being agreed upon this. The familial incidence of this hereditary tendency is placed by the majority of observers at 50 per cent or more. Statistical studies seem to indicate that a history of maternal inheritance is more frequent than that of a paternal transmission.

As to the incidence of migraine, there is some diversity of opinion, some writers placing it much higher than others, the figures varying from 2 per cent to as high as 17 per cent. It is generally agreed, however, that the incidence is considerably higher in women than in men--probably in a ratio of 2 to 1, or higher. The writers are also disagreed in regard to the incidence of migraine in the different classes of society, and to the role that occupation plays, some being of the opinion that it is more prevalent in the upper classes, or among brain workers, while other writers disagree entirely with this view, feeling that caste and occupation have no influence on the incidence of migraine.

"The various theories concerning the causation of migraine still remain unanswered" -- Riley (47). The theories cited in this paper (which most writers consider the significant ones, and the ones worthy of consideration) are:

(1) Vasomotor Theory.--This theory postulates that the symptoms

of migraine are due to a primary alteration in the blood supply (either spasm or relaxation) of the meningeal and cerebral arteries as a result of an altered vasomotor tone. However, the factor which produces a perverted activity of the vegetative nervous system resulting in an abnormal or unbalanced state of vasomotor tone is yet unknown.

(2) Reflex Theory.--This theory postulates that attacks of migraine result from pathology of various organs of the body; this pathology producing reflex irritation throughout the nervous system, especially by way of the vagus nerve and radiating into the trigeminal nuclei, thus producing the headache, nausea, etc. The visual centers are considered by most of the writers on this theory to be the usual offending part of the body producing this reflex.

(3) Central Theory.--This theory assumes that (1) some disturbance within the cerebral cortex itself, or (2) an increase of cerebro-spinal fluid producing pressure upon the dura mater, (this increase resulting from some mechanical obstruction in the cerebral ventricular system), or (3) an angioneurotic increase in fluid secretion and an edema of the brain with the resulting pressure upon the sensitive dura, is responsible for the motor and sensory symptoms of migraine.

(4) Allergic Theory.--This theory is an attractive one, but as Riley (47) says, although it presents a great mass of clinical evidence, it in no way explains the essential mechanism of migraine. It postulates that migraine is an allergic manifestation of a hypersensitive reaction to certain foods.

The theoretical basis for this assumption is the analogy that can be drawn between other known forms of allergy and migraine, such as the hereditary and paroxysmal nature of the attacks, and the fact that migrainous patients also frequently have true allergy.

(5) Toxic-Metabolic Theory.--This theory supposes that migraine is produced as the result of the absorption of various toxins, either exogenous or endogenous, these toxins setting in motion certain processes in the body which result in the various sensory and motor manifestations which occur in the migraine syndrome. Acute and chronic infections, as well as toxic products resulting from altered metabolism within the body, are supposed to produce the condition.

(6) Hypophyseal Theory.--The basis of this theory is that there is an anatomical abnormality of the sella turcica, which, when the anterior portion of the pituitary gland undergoes enlargement (as it is assumed that it does at times, either physiologically or pathologically), inhibits expansion of the gland with resulting pressure symptoms from surrounding nervous tissue and nerve trunks. This theory and the endocrine theory are closely related.

(7) Endocrine Theory.--In this theory, an upset of hormonal balance within the body is supposed to account for the production of migraine. The pituitary gland, of course, is the main gland implicated in this dysfunction, but also the ovaries and the thyroid. Mechanical effects from enlargement of the hypophysis are secondary, according to this theory. There is

considerable evidence at the present time that patients with migraine do present demonstrable changes in hormonal balance, but writers are fairly well agreed that the evidence is not yet complete enough to allow logical conclusions to be drawn.

Thus we see that as yet no one theory as to the cause of migraine is generally accepted by a majority of the men who have worked upon the subject. In fact, the literature on the etiology of the affection is a maze of different and often contradictory hypophysis, many of them seemingly logical, but all of them unproven as yet.

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